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The effectiveness of ultra clean air operating theatres in the prevention of deep infection in joint replacement surgery.

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Background

The development of reliable surgical techniques for total joint replacement is one of the greatest medical ~~developments~~ advancements of the past fifty years. Early in the ~~development~~ inception of joint replacement it became apparent that deep infection is a serious problem in patients who have this type of large surgical implant.

The vital importance of preventing deep infection in joint replacements is principally a matter of the dreadful effects of the infection, and its subsequent treatment, on the patient involved. There are major costs involved both in hospital treatment, in social care and lost economic activity [1,2]. The problem may be made significantly worse in the future by the development of multiply drug resistant bacteria. This is an area where prevention of infection is of the utmost importance, due to the increased difficulty of treating deep implant infections caused by drug resistant bacteria.

The issue was of considerable importance to Sir John Charnley who found an infection rate of 7% in the earliest days of total hip replacement in 1960, using a conventional operating theatre. Charnley appreciated that airborne contamination in a conventional operating theatre was likely to be important so he looked for an engineering solution to provide an ultraclean air environment.

Engineering background

Charnley worked with Hugh Howorth to design an ultra clean air (UCA) operating theatre. The first prototype, known as the "Greenhouse", was installed at Wrightington hospital and further prototypes followed. The Downflow operating theatre developed by Howorth, working with John Charnley, was provided with cotton diffusers, which produced a fairly uniform pattern of flow because the operating chamber had walls. Subsequent designs used partial walls to reduce constraints on the surgical team. In order to optimise the function of partial walled enclosures, Howorth increased the air velocity in the centre of the enclosure to produce a trumpet shape of airflow [3,5].

The use of a uniform down flow of air in ultraclean rooms was originally introduced by Willis Whitfield at the Scandia laboratory, who held the original patent-[34]. It is also possible to use a horizontally orientated air flow operating room and achieve low infection rates [36] but this type of enclosure causes some organisational difficulties and is not widely used.

The use of the term "Laminar flow operating theatre" is inaccurate in engineering terms, as the airflow in operating theatres of all designs is turbulent. Laminar flow will occur, for example in a pipe, when the fluid concerned moves in parallel layers with no movement or disruption between the layers. In a typical pipe the flow is faster in the middle of the pipe and slower next to the walls due to a frictional boundary layer. As the velocity of flow increases the flow is more likely to become turbulent. The velocity at which the flow becomes turbulent is described using Reynolds number, a concept introduced by Osborne Reynolds in his seminal paper of 1883[xx]. ~~(reference needed).~~ In this context, the Reynolds number is defined as the product of the fluid velocity and the width of the conduit through which it travels, divided by the fluid kinematic viscosity.

Comment [MS1]: Added at the end

In an ultra clean air operating theatre that is compliant to UK Health Technical Memorandum HTM 03-01, the down flow air velocity is 0.38 m s~~MS~~$^{-1}$ under the canopy. At this velocity, assuming a typical canopy width of several metres and with the kinematic viscosity of air being approximately 1.5×10^{-5} m^2 s^{-1} the Reynolds number is of the order of 100,000 which exceeds Reynolds criterion for onset of turbulent flow in a conduit of Re > 2300 by almost two orders of magnitude, thus~~is so high that~~ the flow must be turbulent and not laminar.

Comment [MS2]: I have assumed flow in a box of width of a 4 metres in working out these numbers, i.e. the flow is confined by the Perspex side walls of the canopy. It might be helpful if we can refer to imaging studies in op theatres which show that the flow is turbulent in case people aren't prepared to take our word for it.

The airflow pattern in some down flow ultra clean air enclosures is faster in the centre of the operating area than towards the periphery. This is not the same as laminar flow because the increased airflow in the centre is however generated by fans and ducting rather than the developing~~by a~~ boundary layer effect.

It is possible to describe the systems in current use as linear airflow systems, providing ultraclean air [33] or simply as Ultraclean Air Operating Theatres.

The use of linear airflow ventilation systems for operating theatres has a sound basis in engineering science [37] Design approaches involving combinations of practical experimentation and computational fluid dynamics have highlighted the considerable importance of issues such as the movement of personnel [38] and operating table and lamp design [39]

Microbiology background

Charnley subsequently undertook a landmark study, which related reducing airborne contamination to a reducing deep infection rate as the system developed-[3]. The study involved both air sampling with a slit and settle plates. Settle plates were exposed for a period of one hour both on the instrument trays in the clean zone and in the periphery of the operating theatre. Standard slit samplers were used in the periphery of the operating theatre and a special 7-

inch plate slips sampler, with a sterile hose was used to sample air near to the wound.

At the start of the study the contamination rate on the instrument trays was 70 colonies per 90 mm settle plate per hour, by the end of the study it had been reduced to 0.2 colonies per hour. The study showed that as the ventilation and microbiological performance of the operating room was improved the infection rate was gradually reduced from 7% to 0.5%.

The use of ultraclean air enclosures was found to be associated with a significant reduction in deep infection in a large randomised controlled trial conducted by the UK Medical Research Council (MRC). [4-6]

The relationship between airborne contamination and the deep infection rate was confirmed by data from other centres, which were acquired during the later MRC trial. The randomised trial of the use of clean air was supplemented by detailed microbiological studies, which were presented in a separate paper. [6]
The data show that some types of operating theatre, down flow theatres with walls, perform better than others and that the use of body exhausts also reduces contamination during surgery and that lower bacteriological contamination rates correlated with lower deep infection rates.

The MRC trial included 19 centres in three countries, with each centre using both conventional and UCA theatres. There were a total of six different UCA systems in use across the centres. The same surgeon performed operations in both conventional and UCA theatres which, to some degree provides protection against confounding by surgeon.

The papers give scant detail of the precise definition used for deep infection, they were classified into no, some, and strong evidence using criteria of isolation of a pathogen, and a variety of symptoms. Of the 86 infections used in the analysis, 70% had a relevant pathogen isolated from the site. The cumulative incidence in the operations performed in conventional theatres was 1.5 per 100 operations, and in the UCA theatres 0.6 per 100 operations.

In each UCA system there was a reduced incidence of deep infections compared to the conventional theatres in those centres. This provides evidence of consistency in the efficacy of UCA theatres across a range of UCA systems in use at that time.

There are some criticisms that could be made of the trial design. The MRC trial has been criticised because the patients were not randomised for antibiotic prophylaxis. This factor was taken into account when the trial was designed, but it was not fully controlled [5].
The method of randomisation was not completely consistent across the centres, and at one centre it was impractical to operate on both sides in the UCA theatre.

Where non-adherence to the randomisation procedure occurred these operations were excluded.

The statistical comparison of infection rates could be considered to be naive compared to modern standard approaches for multicentre trials. No account was allowed for the between centre heterogeneity in infection rate as would be the norm today. Thus, the significance of the results would be reduced somewhat if such an analysis had been performed compared to the "data lumping" analysis that was performed.

On balance, the trial appears to have been performed to an acceptably high standard, and even if it were re-analysed using modern approaches it would almost certainly provide conclusive evidence of efficacy for UCA systems.

Recent evidence

Recently there has been some worrying evidence that the deep infection rate is not improving and may actually be getting worse, although this trend may be partly related to improvements in diagnostic accuracy [7]. The problem of deep infection is likely to become more intractable due to the rise of multiply resistant bacteria, which may render antibiotic prophylaxis less effective in joint replacement surgery and increase the difficulty of treating any infections which do occur [8].

Recent evidence from New Zealand Joint Registry data [9] and German Krankenhaus (Hospital) National Nosocomial Infection Surveillance System (KISS) Registry data [10] has called into question the usefulness of UCA theatres in preventing deep infection.

A meta-analysis by Bischoff [11] suggests that "the available evidence shows no benefit for laminar airflow compared with conventional turbulent ventilation of the operating room in reducing the risk of SSIs in total hip and knee arthroplasties".

The World Health Organisation (WHO) [12] has made a conditional recommendation that "Laminar flow ventilation" should not be used to reduce the risk of SSI for patients undergoing total arthroplasty surgery, but notes the "very low quality of the supporting evidence".

The use of registry data

The most important concern about the conclusions reached by the WHO is that they have been derived from registry data. Registry data is widely used in orthopaedic surgery but it is known to under record infection rates [13], particularly if the patient does not undergo revision surgery.

Another difficulty with using registry data is the endpoint of the study. In the MRC trial every patient had a form filled in at a mean follow-up of 2.5 years, minimum one year, post surgery and the lost to follow-up numbers were very small.

If the endpoint of a registry based study is revision for infection at six months many later infections will be missed [14]. Early infections arising from severe wound infections will be included whereas some low-grade infections from airborne contaminants will be excluded. Since these late presenting cases are the infections, which are likely to be prevented by UCA theatres the study will tend to underestimate the benefits of ultra clean air.

The KISS study does not provide details of how post discharge surveillance is carried out, and it recognises that it is not performed systematically [10]. The New Zealand registry study uses an endpoint of revision for infection at six months [9]. The registry also only records 63% of infections [15].

The England, Wales and Northern Ireland National Joint Registry (NJR) contains details of over one million operations and it has been useful for monitoring trends in prostheses and clinician performance. Comparisons between orthopaedic procedures, such as unicondylar knee replacement and total knee replacement, are not credible when based on NJR data alone because insufficient data is collected.

The data sets used to collect registry information are not validated and this should be taken into account when drawing conclusions about issues such as thromboprophylaxis regimes and infection prevention regimes. Registry data is intrinsically unreliable when it comes to recording deep infection rates because of the fact that deep infection often presents late and diagnosis is difficult. Over interpretation of the data has therefore to be avoided at all costs [16]

Comparisons were between hospitals with laminar flow and those with conventional ventilation, rather than comparisons within the same hospital. This may lead to major confounding by factors such as differences in hospital/surgeon volume, characteristics of admitted patients and/or the extent of implementation of other SSI prevention measures [17].

The observational data provided by the registries is inevitably weaker than well planned multi-centre prospective data, collected for a specific purpose and far weaker than randomised controlled trial data. The quality of evidence provided by case series data cannot be uprated by using it in a Meta analysis [18].

Uprating up the quality of case series evidence is only appropriate when there is a large or a very large magnitude of effect, when there is an evidence of a dose–response gradient or when consideration of all plausible residual confounders and biases would reduce a demonstrated effect, or suggest a spurious effect when results show no effect [19] None of these factors are present in infection data derived from registries.

There is much literature on the difficulties of estimating causal effects in observational studies [20] and several analytical approaches have been proposed to assist in such endeavours, e.g. propensity score adjustment. An important point is the possibility of bias in the estimate due to confounding factors. Whilst randomisation provides balances for all confounders between comparison groups, there is no such guarantee that confounder variables will have the same distribution in each group being compared. When confounders are measured in the study it is possible to attempt to remove the influence of the effect of interest, one often used approach being to include these in regression models.

Explanations of registry data

The reasons for the apparently counter-intuitive findings, that cleaner air does not equate with fewer infections, are speculative but there are suggestions that either failure to maintain patient normothermia [10] or operating room discipline [22] could have associations.

The retrospective analysis of data in the German National Nosocomial Infection Surveillance System (KISS) by Brandt unexpectedly showed a higher incidence of major infection in the "Laminar flow" group, [10]

The KISS study did use appropriate regression modelling that takes both the clustered and temporal nature of the data into account and includes a number of potential confounders in this regression model. While this approach enables some control over measured confounders it cannot account for any important confounder, which was not recorded.

Wide variability in infection rates was also a feature in the KISS study. One of the departments undertaking hip joint replacements in a laminar flow operating theatre produced a 7.14% severe infection rate in total hip replacements.

Another notable feature in the KISS study was that infection rates in the laminar flow operating theatres were high in procedures such as appendicectomy and cholecystectomy. These operations do not involve deep implants and the infection rates will not be affected by airborne bacterial contamination. The authors concluded that a hypothesis that may explain this phenomenon is that the ventilation could result in lower intraoperative tissue temperatures in the surgical.

The importance of cooling as a risk factor for infection is well documented. This factor is likely to be important in joint replacement procedures carried out in operating theatres with high volume air flows [23]. Patient cooling can be prevented using warm air blankets and forced air-warming systems. Surgeons may be discouraged from using this type of warming either because of time and budget constraints or because of anxieties about disturbing the airflow in the

operating theatre [24]. It is however possible to safely use forced air warming systems, carefully isolated from the general operating room air flow by sheets, taped to the patient.
Most studies show that this type of warming system does not significantly disrupt the airflow in a laminar flow operating theatre [25,26], whereas mechanical obstructions have a major effect [27]. The FDA has recently concluded that maintaining normothermia and that warming devices, including forced air-warming blankets should be used [28].

As described in Orsini et al [29] it is relatively simple to assess the impact of an unmeasured confounder on an epidemiological association. The data on severe SSI rates for hip prosthesis in Brandt of 0.903 per 100 operations in conventional theatres and 1.370 per 100 operations in UCA theatres, The data has been used to explore the impact of a unmeasured confounder, such as hypothermia, on the incidence rate ratio.

Severe SSI	UCAOT	COT	Total
Yes (rate %)	242 (1.371)	99 (0.903)	341
No	17415	10867	28282
Total	17657	10966	28623

Table 1: Approximate data abstracted from Brandt

The data in Table 1 shows an incidence rate ratio of 1.518 (95% CI 1.203 to 1.916). The data were analysed using a proportion of hypothermia of 0.2 (20%) in UCA theatres, and 0.01 (1%) in conventional theatres, and a incidence rate ratio of 3 for hypothermia, i.e. the incidence of severe SSI is 3 times greater in those patients with hypothermia compared to normothermia. These parameters are at the extreme range of those published and were deliberately chosen in order to provide the maximum reduction in the observed association observed in Table 1.

Using the above the externally adjusted incidence rate ratio for UCA theatres is 1.09, a percentage bias of 39%. While adjusting for hypothermia using the above assumptions does remove the unfavourable association between UCA and severe SSI, but it doesn't reverse the direction of the association such that UCA theatres have a protective effect on severe infections.

Current practice

There is much information in the literature which shows that UCA theatres have considerably better microbiological performance than conventional theatres. The microbiological assessments in the MRC trial showed an average of 162 CFU m^{-3} in the conventional theatres and 7 CFU m^{-3} in the UCA theatres. The lowest air counts, 0.54 CFU m^{-3} were obtained when UCA theatres with walls were used with body exhausts [5].

A multicentre study was carried out to review the microbiological performance of operating theatres used for joint replacement surgery in Italy [30].
This study compared the microbiological performance of 16 unidirectional airflow operating theatres to 10 operating theatres using mixed or turbulent airflow. The authors do not fully describe the ventilation systems. Air contamination measured by settle plates was lower in the unidirectional airflow operating theatres but there was very wide variation in the performance of all of the operating rooms, with several of the unidirectional airflow theatres achieving worse results than the mixed or turbulent operating theatres. The best results in the study were obtained in one of the unidirectional theatres in a unit performing a very large number of operations.

In a similar study comparing the microbiological performance of three operating theatres in Besançon it was found that the best performing room was the one with laminar flow [31] In an early study it was found that vertical laminar flow was microbiologically better than horizontal laminar flow and it was 35-90 times better than a plenum ventilated theatre [32].

Conclusions and recommendations

In conclusion we are left with a set of information from the registry studies, which it is quite difficult to explain. There are some explanations for this observation such as hypothermia and disturbances of airflow but bacterial infection is multifactorial and it is difficult to escape the conclusion that there may be some unknown unknowns operating here.

In spite of the large numbers of cases recorded in registries randomised controlled trials remain the gold standard for clinical decision-making. The only RCT that we have in this area supports the use of UCA operating theatres.

There have been many changes and advances in joint replacement surgery since the 1970s but many of the fundamentals have remained the same, so the MRC trial continues to be relevant. The trial should not be ignored simply because it was undertaken a long time ago.

The earliest randomised controlled trial in medicine was carried out by Dr James Lind to show the effectiveness of lemon juice in preventing scurvy in the Royal Navy [21].The result of this trial is just as relevant in a nuclear submarine in 2018 as it was in a sailing ship in 1752.

UCA operating theatres have a microbiological performance, which is around 20 times better thaen conventional theatres, but they are not associated with a 20-fold reduction in infection rates in clinical practice. Part of the reason for this is the fact that the relationship between air contamination and the deep infection rate is logarithmic, it is necessary to achieve a ten fold reduction in air contamination in order to halve the infection rate [6].

The most common infecting organisms in joint replacement surgery are skin organisms [41]. It is reasonably well established that airborne contamination due to human skin scales, from operating theatre staff, which carry bacteria (colony-forming units or CFUs) correlates with subsequent deep infection [3,6]. It is likely that that these can settle on surgical instruments, implants or in the wound and cause deep infections, but there may be other mechanisms involved.

The use of ultra clean air systems has been shown to reduce contamination on surgical instruments [40]. It is possible that part of the reason for Charnley's excellent infection rates was the use of multiple instrument trays for different stages of the operation so blood contaminated instruments are only exposed to the theatre air for a minimum length of time. This and other areas of operating theatre practice, such as different types of headwear and body exhaust which require further evaluation.

In order to make progress it makes sense to improve the quality of data collection by joint registries and other surveillance systems and to use this data to identify the characteristics of units, which achieve low infection rates. In particular it would be valuable to reanalyse the KISS data from this point of view. The use of NJR data to give advice on the value of UCA theatres is not practical because the vast majority of joint replacements in the UK are carried out in UCA theatres. NJR data may however be valuable in identifying the characteristics of high performing units. Our aim should be to bring all joint replacement units up to the standards of the very best.

In the UK, the National Institute for Health Research (NIHR) has funded health protection research units in healthcare associated infection and antimicrobial resistance. One of the main themes of these research remits is to promote behavioural change in healthcare staff, which is clearly important if ultraclean air ventilation systems are to be used to their full potential.

We would support this approach, which emphasises behavioural factors. These factors are clearly important, as demonstrated by the wide variability in microbiological performance and infection rates recorded in the literature.

There is some evidence that modifying behaviour is effective in reducing bacterial contamination [42,43] and that modifying behaviour is a multidisciplinary problem [44].

Modifying behaviour will only be effective if we know exactly what behavioural factors make a difference to deep infection rates. Further research on the effect of behaviour and environmental factors in all types of operating theatre is clearly indicated. It is very difficult to evaluate individual factors using controlled trials. The reason for this is that when infection rates are already very low large numbers of patients, up to 10,000, would be required to produce an answer for each factor.

Engineering research should use a combination of airflow measurement and visualisation techniques to analyse the function of current designs of operating theatre. Engineering techniques should identify designs of operating theatre, which minimise the possibility of contamination occurring during contemporary joint replacement surgery, in the context of current operating theatre practice.

The idea that operating in dirty air might be associated with a lower infection rate than operating in clean air does not come easily to either orthopaedic surgeons or microbiologists. The microbiological data convincingly shows that there is a relationship between airborne contamination and deep infection rates. Ultraclean air ventilation can produce very low bacterial contamination rates but UCA theatres are complex systems where minor failures in technique can result in detrimental effect on air-quality and therefore jeopardise the safety of patients [43,45].

If used correctly, UCA theatres offer the safest possible environment for joint replacement surgery. If they are not used correctly they are no better than a conventional theatre and, under some circumstances, they may actually be worse.

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